# Quantify White Matter Damage with Confounding Fiber Crossing and CSF Contamination

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**Target Audience:** This work is for those who are interested in employing diffusion MRI to assess white matter integrity in CNS diseases.

**Purpose:** Diffusion tensor imaging (DTI) has been shown to detect and distinguish axon and myelin injury in coherent white matter tracts based on decreased axial diffusivity (AD) and increased radial diffusivity (RD) respectively.[1-3] However, fiber crossing and cerebrospinal fluid (CSF) contamination has been shown to significantly reduce the sensitivity and specificity of DTI in detecting axon and myelin injury. Appropriate modeling of diffusion weighted MRI signals to resolve and quantify the effect of crossing-fibers and CSF contamination to accurately assess AD and RD of individual fiber tracts is crucial in maintaining the specificity of AD and RD. Historically, AD and RD of individual fiber tracts was not computed after resolving crossing fibers.[4,5] In addition, MS lesions are frequently periventricular[6,7], and CSF contamination is significant in these lesions. In this study, we examine the capability of recently developed diffusion basis spectrum imaging (DBSI) to model structural confounds (CSF contamination and crossing fibers), obtaining accurate AD and RD for individual fiber tract in human white matter.

**Method:** Subjects: Procedures involving human subjects were approved by the Institutional Review Board of Washington University. Five healthy control subjects and one MS patient were imaged. MRI: A 3-Tesla TIM Trio scanner (Siemens, Erlangen, Germany) was employed. Diffusion MRI data were collected at 2x2x2 $mm^3$ resolution with TR/TE = 10000/120ms. The max b-value was 2000 $s/mm^2$. The 99-direction diffusion scheme was employed for total 15 minutes acquisition time. High-resolution 1x1x1 $mm^3$ sagittal FLAIR images were used for MS lesion identification. DBSI/DTI Analysis: A voxel-based DBSI analysis was performed based on the recent publication.[5] Conventional DTI was also computed. ROI Selection: In each healthy subject, a ROI representing pure white matter tract was selected at the center of the corpus callosum (CC), and a ROI with CSF contamination (partial volume effect) was selected in the CC bordering lateral ventricle. Similarly, representative voxels was selected at the point where the corona radiata (CR) crosses the CC, and also at the pure CC and CR. In the particular case of one MS lesion located at the crossing of corpus callosum (CC) and cingulum, bordering the ventricle, six voxels were examined; three located within the FLAIR-identified lesion itself, and three outside of the lesion. The first voxel within the lesion was selected in the region where fibers of the CC crossed those of the cingulum. The second voxel was selected entirely in the CC region within the lesion. The third voxel within the lesion was selected such that it bordered the lateral ventricle. The other three voxels were distributed within the corpus callosum, but outside of the FLAIR-defined lesion sequentially further from the lesion. Fiber Tractography: Modified whole brain streamlines fiber tracking[8] was conducted using DBSI fiber orientations. DBSI fiber faction controlled tract termination.[9]

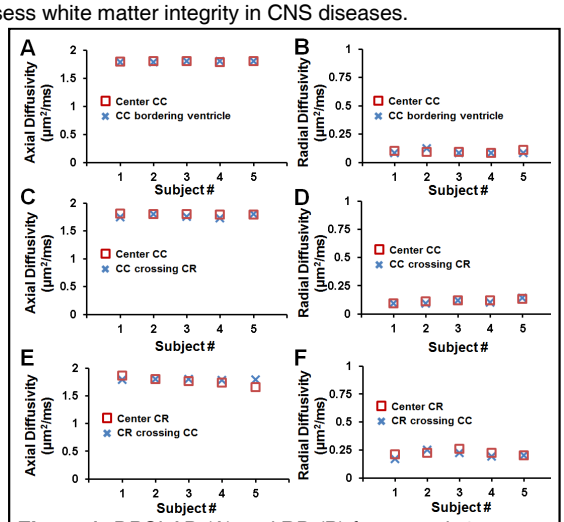


**Figure 1:** DBSI AD (A) and RD (B) from voxels in central CC and in CC bordering the lateral ventricle were in agreement. DBSI AD (C) and RD (D) from central CC compared with CC data from CC/CR crossed region. DBSI AD (E) and RD (F) from central CR compared with CR data from CR/CC crossed region.

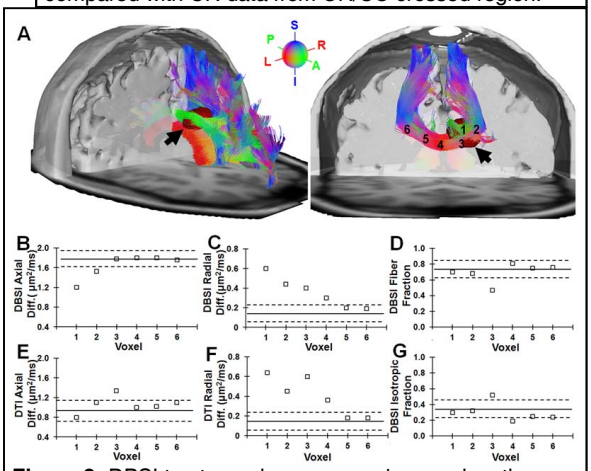


**Figure 2:** DBSI tractography was superimposed on the FLAIR image to show the location of the lesion (dark red, A left). Six voxels were labeled on CC (see text, A right). DBSI AD (B) showed reduction in voxels 1 and 2. DBSI RD (C) increased most in voxel 1, also elevated in voxels 2, 3, and 4. DTI AD (E) and DTI RD (F) failed to reflect monotonic spatial changes, especially in voxels 1 and 3. Lack of reduction in fiber fraction in voxels 1 and 2 (D) suggested little to no loss of axons. Increased isotropic fraction in voxel 3 indicated contamination from CSF (G).

**Results and Discussion:** Comparisons of ROIs selected in center of CC with ROIs selected partly in the CC and partly in the ventricle were performed in five healthy controls (Fig. 1A B), with DBSI AD and RD derived: AD = 1.79 ± 0.011 vs. 1.79 ± 0.009 $\mu m^2/ms$ and RD = 0.088 ± 0.018 vs. 0.094 ± 0.012 $\mu m^2/ms$ for the pure and CSF-contaminated fiber tracts, respectively. The comparison between the pure CC diffusion results to those within the CC at the region of CR crossing (Fig. 1C D) showed AD = 1.80 ± 0.01 vs. 1.76 ± 0.03 $\mu m^2/ms$ and RD = 0.11 ± 0.02 vs. 0.11 ± 0.02 $\mu m^2/ms$, respectively. Similarly, for pure CR and for CR fibers extricated from the region of crossing with the CC (Fig. 1E, F), AD was 1.76 ± 0.08 vs. 1.79 ± 0.01 $\mu m^2/ms$ and RD was 0.23 ± 0.03 vs. 0.20 ± 0.03 $\mu m^2/ms$. DBSI was also performed on the large lesion located at the intersection of the CC and cingulum in a MS patient. Tracts were superimposed on FLAIR image (lesion is dark red in Fig. 2A; left, black arrow). Decreased DBSI AD was confined to voxels 1 and 2 within the lesion (Fig. 2B), whereas increased DBSI RD was seen not only in voxels 1, 2 and 3 within the lesion, but also in voxel 4 (outside of the FLAIR-defined lesion) within normal-appearing CC nearest to the lesion (Fig. 2C). DBSI fiber fraction (Fig. 2D) was within the normal range except voxel 3 with significant CSF contamination (Fig. 2G). Likely due to the confounding effect of crossing fibers and CSF contamination, DTI derived AD failed to detect axonal injury inside the lesion (Fig. 2E). DTI derived RD increased in a trend similar to that of DBSI-derived RD with different extent of change (Fig. 2F). Solid and dashed lines are the mean values and standard deviations from a gender/age matched healthy subject.

**Conclusion:** DBSI provides a novel way to accurately quantify white matter damages in the complication of crossing fibers and CSF contamination.

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